Michigan Department of Community Health

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Identification of Birth Defects in Michigan Infants with Sickle Cell Disease and Sickle Cell Trait: MI NBS and MBDR Data, 2004-2006

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Introduction

The Michigan Birth Defects Registry (MBDR) is a passive surveillance system, relying on case reporting from hospitals, labs, and genetics clinics. The MBDR also relies on case sharing from programs such as the Newborn Screening (NBS) Program. The NBS Program has been screening all newborns for sickle cell disease (SCD) since 1987 and all SCD cases are reported to the MBDR. Little research has been done to assess anomalies associated with SCD or sickle cell trait (SCT). A joint analysis with NBS and MBDR has never been done before for validation and quality improvement purposes or for a comprehensive health status assessment.

Research Questions

1. How many children with SCD are missing or misclassified in the MBDR compared to NBS records?

2. What birth defects are reported in children with SCD or SCT?

Methods

Source of Data and Study Design: This is a retrospective cross-sectional study linking Michigan Birth Defects Registry (MBDR) data to the Newborn Screening (NBS) data for birth years 2004 to 2006. Both data sources are routinely linked to live birth records through probabilistic linkages. The birth certificate number served as the unique identifier so that the MBDR and NBS records could be deterministically linked. Medical charts were reviewed to verify diagnosis for any discrepant findings in the MBDR compared to NBS records.

Source Population and Variables: Resident infants born in Michigan from 2004 to 2006 who were diagnosed with either SCD or SCT by NBS. SCD and SCT definitions were taken from the International Classification of Diseases 9th Revision Clinical Modification. ICD-9 Codes for SCD included 282.6 through 282.69 while 282.5 was used for SCT.

Statistical Analysis: The linked MBDR-NBS file was used to identify missing or misclassified SCD cases in the MBDR. The positive predictive value (PPV) and sensitivity (Se) for the MBDR were determined, using NBS as the gold standard for SCD diagnoses. The relative risk of having a birth defect in addition to SCD or SCT compared to those without the blood disorders was determined for having any birth defect as well as for each major category of birth defects. Race-specific relative risks were also calculated. SAS v.9.1 was used for statistical analysis.

Results – Case Validation

•186 SCD cases were identified by NBS of which 100% were linked to live birth records.

•8,728 SCT cases were identified by NBS of which 8,446 (96.8%) were linked to live birth records.

•**Positive predictive value (PPV)** = (166/263) = 0.63

•**Sensitivity (Se)** = (166/186) = 0.89

Table 1: SCD case classification with NBS as the gold standard (true diagnosis).

MBDR	NBS (Gold Standard) Case (SCD)	NBS (Gold Standard) Non Case (No SCD)	Total
Case (SCD)	166 True Positives (TP)	97 False Positives (FP)	263
Non Case (No SCD)	20 False Negatives (FN)	NA True Negatives (TN)	20
Total	186	97	283

•Medical charts were reviewed for 60 (70.1%) of the 97 false positives.

- •2 cases were **true** SCD cases *(both had been reported to have SCD by NBS but were incorrectly recorded as SCT in the follow-up database)*
- •29 had a normal newborn screen
- •5 had an abnormal screen for hemoglobinopathy and 2 had inconclusive newborn screens, but no additional information
- •14 had no NBS or SCD information
- •8 had some other diagnosis:
  - •4 other thalassemia; 1 severe anemia; 1 iron deficiency; 2 sickle cell trait

Results – Additional Anomalies

SCD Cases

•A total of 168 true SCD cases were identified through NBS and the MBDR (n=166) and medical chart reviews (n=2).

•Among linked MBDR-NBS SCD cases, approximately 12% (n=20) had an additional major anomaly.

•95.8% (n=161) of the SCD population was black.

•The risk of having any birth defect was 1.7 (95% CI: 1.1, 2.7) times higher and the risk of having an integument defect was 7.1 (95% CI: 3.2, 16.1) times higher in those with SCD, compared to those without SCD (Table 2).

- ***Neither association achieved significance when stratified by race.***

SCT Cases

•There were a total of 8,444 SCT cases identified through the MBDR-NBS linkage and medical chart reviews.

•77.4% (n=6,532) of the SCT population was black and of those who were black, 11.5% (n=753) had an additional anomaly.

•17.6% (n=1484) of the SCT population was white and of those who were white, 8.2% (n=121) had an additional anomaly.

•For **blacks**, the risk of having a digestive defect was 1.6 (95% CI: 1.2, 2.0) times higher in those with SCT, compared to those without SCT (Table 3).

•For **whites**, the risk of having a musculoskeletal defect was 1.7 (95% CI: 1.3, 2.3) times higher for those with SCT compared to those without SCT (Table 3).

Table 2: Estimated effect of SCD on the risk of having a birth defect: MI MBDR-NBS Data, 2004-2006

Defect Category	Rate in Michigan†	Rate in SCD Population†	Crude RR	Crude 95% Confidence Interval
Any Defect	740.9	1190.5	**1.7**	**(1.1, 2.7)**
CNS	47.6	*		
Eye	33.0	*		
Ear/Face/ Neck	18.4	*		
Heart	205.4	357.1	1.8	(0.8, 4.0)
Respiratory	65.1	*		
Cleft Palate, Lip	16.0	*		
Alimentary Canal/Digestiv	57.1	*		
Genital/Urinary	162.5	*		
Musculoskeletal	187.9	*		
Integument	51.8	357.1	**7.1**	**(3.2, 16.1)**
Chromosomal	22.5	*		
Other/Unspecified	44.8	*		

†Rates are per 10,000 live births
*Indicates less than 5 cases

Table 3: Estimated effect of SCT on the risk of having a birth defect: MI MBDR-NBS Data, 2004-2006

Defect Category	Black Population RR	Black Population 95% Confidence Interval	White Population RR	White Population 95% Confidence Interval
Any Defect	**1.1**	**(1.0, 1.2)**	**1.3**	**(1.0, 1.5)**
CNS	1.3	(0.97, 1.6)	0.92	(0.41, 2.0)
Eye	0.93	(0.59, 1.5)	0.39	(0.10, 1.6)
Ear/Face/ Neck	0.92	0.54, 1.6)	1.1	(0.37, 3.5)
Heart	1.0	(0.88, 1.1)	1.2	(0.83, 1.7)
Respiratory	1.1	(0.84, 1.4)	1.3	(0.70, 2.3)
Cleft Palate, Lip	0.96	(0.50, 1.9)	1.2	(0.40, 3.8)
Alimentary Canal/Digestive	**1.6**	**(1.2, 2.0)**	0.81	(0.39, 1.7)
Genital/Urinary	0.95	(0.78, 1.2)	1.3	(0.93, 1.9)
Musculoskeletal	1.1	(0.95, 1.2)	**1.7**	**(1.3, 2.3)**
Integument	1.1	(0.93, 1.3)	0.98	(0.32, 3.0)
Chromosomal	0.81	(0.47, 1.4)	0.60	(0.15, 2.4)
Other/Unspecified	0.99	(0.69, 1.4)	1.4	(0.72, 2.7)

Discussion

•Through identification of missing and misclassified cases, the MBDR-NBS linkage can help improve program efforts in reporting and follow-up processes.

- Hospital training and education on reporting of SCD and SCT cases to the MBDR may be needed.

•Infants with SCT and SCD may have increased risk of having additional birth defects.

- Increased referral services may be needed for those with SCT or SCD, and families may need information about available resources for their children.
- Further research is needed to expand knowledge of birth defects associated with SCD and SCT.

Future Directions

•Conduct more analyses that control for additional factors such as maternal age, prematurity and birth weight.

•Expand validation between MBDR and NBS to other disorders in NBS panel.

Acknowledgements

•**Lorrie Simmons, RHIT,** *Quality Improvement Coordinator, Michigan Birth Defects Registry*

•**Glenn Copeland, MBA,** *Director, Michigan Birth Defects Registry*

Resources

Michigan Birth Defects Registry (MBDR) Data, 2004-2006.

Linked Michigan Birth Defects Registry (MBDR) Data and Newborn Screening and Follow-up (NBS) Data, 2004-2006.

Hart AC, Stegman MS, Ford B, eds. *International Classification of Diseases 9th Revision Clinical Modification, 6th Edition.* Ingenix 2009.

Washington University School of Medicine. Low blood oxygen may lead to heart defects in children with sickle cell disease. Science Daily. 5 May 2010. Retrieved November 15, 2010, from <http://www.sciencedaily.com/releases/2010/04/100427171808.htm>

Steiner LA, Gallagher PG. Erythrocyte Disorders in the Perinatal Period in Adverse Pregnancy Outcome and the Fetus/Neonate. *Semin Perinatal.* 2007; 31(4): 254-261.

Funded in part by grant no. DD10-100102 from the Centers for Disease Control and Prevention, NCBDDD.